Cryopreservation and transplantation of ovarian tissue exclusively to postpone menopause – technically possible but endocrinologically doubtful

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Abstract

Transplantation of cryopreserved ovarian tissue has been shown to successfully induce pregnancies and puberty. Thus, using cryopreserved ovarian tissue to postpone menopause („tissue hormone therapy" (THT)) seems to be an interesting option to avoid conventional menopause hormone therapy (MHT). However, pregnancy induction and replacing MHT by THT are completely different topics as different requirements need to be met. First, MHT requires long lasting and continuous hormone production. It still needs to be proven if the transplanted tissue is active for at least 5 years with a continuous follicle growth to avoid phases with low estrogen production which would otherwise cause menopausal symptoms and could reduce the postulated benefit for women`s health. Secondly, the advantage of a physiological hormone production over a non-physiological MHT is still hypothetical. Third, hysterectomized women who do not need progesterone for endometrial protection, would only require estrogens imposing more health benefits (cardiovascular system, mammary

gland) than estrogen/progesterone production or replacement. Therefore, transplanting ovarian tissue exclusively to postpone menopause is endocrinologically doubtful and should only performed within clinical trials

Keywords

Ovarian tissue, cryo-preservation, transplantation, menopause, menopausal hormone therapy

Introduction

Following the first delivery after transplantation of ovarian tissue in 2005, cryopreservation of ovarian tissue has become a widely used option as a fertility preservation technique prior to cytotoxic therapies in women with malignancies. Currently the delivery rate per transplantation is approximately 24% (Liebenthron et al. 2015). However, since ovarian tissue activity remains up to 70% one year after transplantation (Liebenthron et al. 2015), the delivery rate per transplantation is expected to further increase. Furthermore, as only about one third to one half of the cryopreserved tissue is used per transplantation, re-transplantations will be possible in most cases.

Ovarian tissue has also been used to induce puberty in children with ovarian failure due to prior cytotoxic therapy (Ernst et al. 2013), proving that tissue hormone therapy (THT) may induce a sufficient rise in serum estrogen levels, and also may replace exogenous hormone replacement therapy in certain cases.

Thus, a consequential next step would be to use cryopreserved ovarian tissue to postpone menopause instead of applying a conventional menopausal hormone therapy (MHT). As this option has already been suggested by reproductive physicians and biologists without adequately addressing the endocrinological aspects (Andersen and Kristensen 2015), we will focus our discussion on the latter. To better compare both treatment options, we have coined the expression “tissue hormone therapy” (THT) as a counterpart to the commonly known MHT.

Endocrinological aspects

Following the initial results of the Women’s Health Initiative (WHI), a prospective, randomized, placebo-controlled trial (RCT), aiming to assess the risk and preventive factors associated with the most common causes of death, disability and reduced quality of life in postmenopausal women, subsequent subanalyses and RCTs have provided a better picture of

the benefit-risk-profile of MHT (Manson et al. 2013). In the WHI, postmenopausal women with an intact uterus were treated with either conjugated equine estrogens (CEE; 0.625 mg/d) combined with medroxyprogesterone acetate (MPA; 2.5 mg/d) or placebo, while hysterectomized women received either CEE (0.625 mg/d) or placebo, respectively. During the CEE plus MPA intervention phase risk of stroke, pulmonary embolism, invasive breast cancer (BC), and dementia (in women aged ≥ 65 years) was increased while benefits included decreased vasomotor symptoms, hip fractures, and diabetes, respectively (Manson et al. 2013). However, for combined MHT BC risk may differ for various progestogens as the breast profile has been reported to be "safer" for estrogens combined with micronized (natural) progesterone, respectively. Risks and benefits were more balanced during the CEE alone intervention. Importantly, BC risk was non-significantly reduced during the intervention phase becoming significant during cumulative follow-up (Manson et al. 2013). Furthermore, for CEE alone, younger women (aged 50-59 years) had more favorable results for myocardial infarction, all-cause mortality, and the global index (Manson et al. 2013). All these findings clearly demonstrate that MHT is beneficial for women aged around 50-59 years and especially for hysterectomized (no need for a progestagen) menopausal women.

Thus, the key questions arising in the debate about MHT and THT for postponing menopause are 1) if natural late menopause (> age 55), as a model for extended physiological ovarian activity, is beneficial for women's health at all, 2) if THT creates a more physiological hormonal profile and, if yes, 3) whether THT is thus more beneficial than MHT - assuming long-term tissue activity after transplantation.

Late menopause has been associated with, e.g., a decreased risk for coronary artery disease (Barrett-Connor 2013), whereas BC risk was increased (Monninkhof, van der Schouw and Peeters 1999). Accordingly, cardiovascular mortality has been found to be decreased in women with late menopause (Jacobsen, Heuch and Kvale 2000). However, overall mortality has been reported to be decreased (Jacobsen, Heuch and Kvale 2003) or unchanged (Jacobsen, Knutsen and Fraser 1999). Therefore, cardiovascular health will be the main endpoint when considering THT for postponing menopause.

Ovaries produce a broad spectrum of estrogenic, progestagenic and androgenic hormones that are released in a defined pulsatile rhythm. Assumingly but not proven yet, transplanted ovarian tissue produces the same pulsatile spectrum of steroid hormones. However, we do not know if a more physiological steroid hormone profile is more benefical than a fix combination of one or two hormones within a MHT preparation. Furthermore, we do not

know when the optimal time point for ovarian tissue transplantation would be as already slight hormonal changes during perimenopause may be associated with symptoms such as hot flushes, sleep disorders and abnormal uterine bleeding in need for treatment. It might be that transplanted ovarian tissue with only a very small follicle pool will result in a similar but not better hormonal profile compared to the natural menopausal transition warranting additional MHT.

Reproductive aspects

Social freezing to postpone child bearing has also become a topic of interest. So far, it is limited to cryopreservation of oocytes. However, although social freezing is already widely offered and performed, it is still controversial (von Wolff et al., 2015). For example, social freezing may not solve social problems but only postpones them, pregnant women are potentially becoming older leading to higher obstetrical risks and social freezing usually requires in vitro fertilization (IVF) which however has been associated with an increased risk of malformations and functional disorders such as an increased carotis-intima-media-thickness leading to an increased pulmonary blood pressure in mice and humans, respectively (von Wolff et al., 20105). While the increased risk of malformation may be attributed to a general predisposition due to infertility itself, functional disorders, which are probably due to epigenetic modifications, cannot. Therefore, social freezing using ovarian tissue followed by IVF is possibly associated with an increased health risk for the offspring. However, pregnancies may also be achieved after transplantation of ovarian tissue without IVF. Tissue transplanted into the remaining ovary and even into a peritoneal pocket can lead to spontaneous pregnancies (Liebenthron et al. 2015). Thus, cryopreservation of ovarian tissue might also be an interesting alternative of social freezing. However, as data on the technique's efficacy and on children's outcome after having used this technique are still limited, cryopreservation of ovarian tissue to postpone child bearing cannot yet be generally recommended.

Discussion

As life expectancy increases women spend about one third of their lives after menopause, that is, in a state of estrogen deficiency. Considering the predominantly beneficial impact of late menopause and MHT on women's health one might hypothesize that postponing menopause by transplanting previously cryopreserved functioning ovarian tissue may have a beneficial impact on the individual. However, there are some objections to this hypothesis. First,

restoring one organ's function does not necessarily imply a benefit for the whole „biosystem" human being. Secondly, although steroid hormones do play a central role in the aging process, they cannot compensate for other, internal or external, risk factors such as genetic predisposition, lifestyle (e.g. smoking, obesity), social and work place environment. Next, age at initiation of steroid hormone exposure does have an impact. While exogenous estrogens during peri- and early postmenopause have a preventive effect on atherosclerosis progression they have an opposite effect when initiated at later age (> age 60) (Hodis and Mack 2014). Therefore, the impact of THT on women's health will also depend on the timing of transplantation.

Most likely, THT will improve menopausal symptoms which, however, still needs to be scientifically proven. Also, THT will not be easily adaptable in dosage like MHT and might require some additional MHT for menopausal symptom relief. THT will result in the production of estrogens and progesterone which may increase BC risk. However, in hysterectomized women estrogen only therapy would be the preferred treatment choice as it reduces BC risk (Manson et al. 2013). Finally, the duration of tissue activity can neither be estimated nor can the hormone production be reduced or stopped without further surgery. To really compensate for MHT, the transplanted tissue should be active for at least 5 years with a continuous follicle growth to avoid phases with low estrogen production which would otherwise cause menopausal symptoms and could reduce the postulated benefit for women`s health.

Besides the health aspect, cost will also play a role. Accordingly, insurance companies will only reimburse treatments that are beneficial, effective and economically sound. Conventional MHT is quite cheap. In contrast, THT requires two laparoscopies, one for removal of the tissue and one for re-transplantation, and long-term storage of the tissue. Surgery does not only set a woman at health risk but is also more expensive than a MHT.

Thus, THT is a very interesting option to postpone menopause. However, from the endocrinological, economical and the safety point of view it is currently not an alternative to a MHT if tissue is exclusively cryopreserved and transplanted for postponing menopause. If instead, THT was used for both postponing child bearing and menopause the benefit-risk-ratio would shift towards the benefits as the tissue is not removed and stored exclusively for postponing menopause. Therefore, if the efficacy of tissue transplantation to induce pregnancies was further increased, this double strategy could possibly become an alternative option.

Conclusion

Transplanting ovarian tissue to exclusively postpone menopause is currently doubtful from an endocrinological point of view. However, as transplanted tissue has been shown to successfully generate spontaneous pregnancies, and assuming that the activity of the transplanted tissue can be further increased, cryopreservation of ovarian tissue to combine both, social freezing and postponing menopause, might become a feasible option with an acceptable benefit-risk-ratio in the future.

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